Therakos™
ECP Immunomodulation

ECP Guidelines and Recommendations Summary

The THERAKOS™ CELLEX™ Photopheresis System is MDR approved across 5 disease states

The THERAKOS™ CELLEX™ Photopheresis System has obtained CE Certification under the Medical Device Regulation (EU MDR) 2017/745

The THERAKOS™ CELLEX™ System is intended to be used in patients who require the administration of photopheresis. This includes patients suffering from:

- Cutaneous T Cell Lymphoma (CTCL) in patients >18 years of age
- Acute and Chronic Graft versus Host disease (aGvHD, cGvHD) >3 years of age
- Solid Organ Transplant (SOT) rejection (Lung and Heart) >18 years of age

MDR approved for 5 INDICATIONS

Please see Important Safety Information on last page.

DISEASE: **aGvHD**

RECOMMENDATION	SOCIETY/ASSOCIATION	STRENGTH/GRADE	REGION	YEAR
Patients not responding to first-line therapy with corticosteroids[1]	EDF		EU	2020
ECP can be used in patients with SR, SD or SI aGvHD[2]	Nordic ECP Quality Group		Nordics	2020
Second-line therapy in grades II–IV aGvHD in SR, SD, SI patients[3]	UKPS	B (for cutaneous and hepatic), C (for GI and pulmonary)	UK	2017
As second-line therapy for aGVHD, treatment should be started as early as possible[4]	DGHO		DACH	2022
In patients with aGvHD refractory to first-line treatment, ECP is then suggested second-line and subsequent treatment[5]	SIdEM/GITMO		Italy	2024
Second-line therapy of SR aGvHD[6]	BCSH/BSBMT	2C	UK	2012
ECP is listed as one of 14 second-line therapies in patients with SR-aGvHD, with no standard second-line treatment according to these guidelines[7]	EBMT	2A	Europe	2020
ECP recommended as an adequate second-line therapy due to its effectiveness and specially safety profile, mainly in patients with only cutaneous involvement[8]	GETH	2B	Spain	2022

DISEASE: **cGvHD**

RECOMMENDATION	SOCIETY/ASSOCIATION	STRENGTH/GRADE	REGION	YEAR
ECP recommended as a salvage therapy for cGvHD, with a steroid-sparing effect, good tolerance, and a venous access requirement[9]	DGHO		Germany	2023
Second-line therapy in patients with SD, SI or SR cGvHD[1]	EDF		EU	2020
Patients with SR, SD or SI cGvHD[2]	Nordic ECP Quality Group		Nordics	2020
SR/SD/SI cGvHD patients[3]	UKPS	A (for cutaneous), B (for hepatic), D (GI and pulmonary)	UK	2017
In patients with cGvHD refractory to first-line treatment, ECP is then suggested second-line and subsequent treatment[5]	SIdEM/GITMO		Italy	2024
Second-line therapy in skin, oral or liver cGvHD[10]	BCSH/BSBMT	1B	UK	2012
Second-line therapy of cGvHD[11]	EMECC	C1-II	DACH	2011
ECP may be used in first-line in association with steroids (recommendation grade 2C) and is listed as one of 11 second-line therapies in SR-cGvHD (recommendation grade 2B)[7]	EBMT	2B	Europe	2020
ECP recommended as a second-line treatment due to its effectiveness and safety profiles as well as due to the broad clinical experience in patients with cGvHD[8]	GETH	2B	Spain	2022

aGvHD: *acute Graft-versus-Host Disease* ***cGvHD:*** *chronic Graft-versus-Host Disease* ***CNIs****: Calcineurin Inhibitors* ***CTCL:*** *Cutaneous T-Cell Lymphoma*
MF/SS: *Mycosis Fungoides/Sézary Syndrome* ***SD:*** *Steroid-Dependent* ***SR:*** *Steroid-Refractory* ***SI:*** *Steroid-Intolerant*

DISEASE: **CTCL**

RECOMMENDATION	SOCIETY/ASSOCIATION	STRENGTH/GRADE	REGION	YEAR
First-line therapy for erythrodermic MF stage IIIA or IIIB patients, and for stage IVA1 or IVA2 MF/SS patients[1]	EDF		EU	2020
ECP, either alone or in combination with other treatment modalities such as IFNα, retinoids, TSEBT and PUVA, has been suggested as the treatment of choice in SS and erythrodermic MF[12]	ESMO	[IV, B]	EU	2018
First-line in patients with erythrodermic CTCL, stage III and IVA. Maintenance therapy recommended when clinical durable benefit is derived[3]	UKPS	Grade A for erythrodermic (stage III/IVA/B1/0); grade E for nonerythrodermic (stage IA-IIB)	UK	2017
First-line therapy for MF stage III and for SS + maintenance therapy after remission has been achieved[13]	EORTC	Level 3	EU	2023
First-line therapy for erythrodermic MF (stage III) and SS (stage IVA1) (Strength of recommendation C)[14]	British Association of Dermatologists and U.K. Cutaneous Lymphoma Group	No specific strength for ECP as a treatment in the guidelines	UK	2018

IFNα, *Interferon alpha;* ***PUVA,*** *Psoralens plus UltraViolet A;* ***TSEBT,*** *Total Skin Electron Beam Therapy.*

DISEASE: **HEART TRANSPLANT**

RECOMMENDATION	SOCIETY/ASSOCIATION	STRENGTH/GRADE	REGION	YEAR
Recurrent or resistant acute cellular rejection[15]	ASFA	1B	US	2023
Rejection prophylaxis[15]	ASFA	2A	US	2023
Cardiac transplant rejection[13]	UKPS	A	UK	2017
Can be considered for recurrent or resistant rejection[16]	ISHLT	2B	ALL	2023

DISEASE: **LUNG TRANSPLANT**

RECOMMENDATION	SOCIETY/ASSOCIATION	STRENGTH/GRADE	REGION	YEAR
Salvage therapy for lung transplant rejection when conventional therapies do not produce an adequate response[1]	EDF		EU	2021
Chronic Lung Allograft Dysfunction. Bronchiolitis Obliterans Syndrome[15]	ASFA	1C	US	2023

1 Knobler R, Arenberger P, Arun A, et al. European dermatology forum - updated guidelines on the use of extracorporeal photopheresis 2020 - part 1. J Eur Acad Dermatol Venereol. 2020;34(12):2693-2716. doi:10.1111/jdv.16890. Part 2 J Eur Acad Dermatol Venereol. 2021;35(1):27-49. doi:10.1111/jdv.16889. **2** Nygaard M, Wichert S, Berlin G, Toss F. Extracorporeal photopheresis for graft-vs-host disease: A literature review and treatment guidelines proposed by the Nordic ECP Quality Group. Eur J Haematol. 2020;104(5):361-375. doi:10.1111/ejh.13381. **3** Alfred A, Taylor PC, Dignan F, et al. The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis Society. Br J Haematol. 2017;177(2):287-310. doi:10.1111/bjh.14537. **4** Zeiser Robert, Wolff D, Scheid C, et al. Graft-versus-Host Erkrankung, akut Onkopedia July 2024 Accessed January 7, 2024 https://www.onkopedia.com/de/onkopedia/guidelines/graft-versus-host-erkrankung-akut/@@view/html/index.html. **5** Anna C, Marchetti M, Bianco I, et al. Treatment of acute and chronic graft-versus-host disease with extracorporeal photopheresis: update of best practice recommendations from Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and the Italian Transplant Group for Bone Marrow Transplantation, Hematopoietic Stem Cells and Cell Therapy (GITMO) Transfusion and Apheresis Science. 2024;63(5):103990. doi:10.1016/j.transci.2024.103990. **6** Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. Br J Haematol. 2012;158(1):30-45. doi:10.1111/j.1365-2141.2012.09129.x. **7** Penack O, Marchetti M, Ruutu T, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol. 2020;7(2):e157-e167. doi:10.1016/S2352-3026(19)30256-X. **8** Martinez C, Solano C. [GVHD Comprehensive Clinical Practice Guideline]. Spanish Group of Hematopoietic Transplantation and Cellular Therapy (GETH-TC) March 16, 2022 Accessed January 7, 2025 https://www.geth.es/component/content/article/242-guias/711-guia-de-practica-clinica-integral-de-la-eicr?Itemid=437. **9** Wolff D, Zeiser R, Scheid C, et al. Graft-versus-Host Erkrankung, chronisch Onkopedia January 2023 Accessed January 7, 2024 https://www.onkopedia.com/de/onkopedia/guidelines/graft-versus-host-erkrankung-chronisch/@@guideline/html/index.html. **10** Dignan F.L., Amrolia P., Clark A., et al. Diagnosis and management of chronic graft-versus-host disease Br J Haematol. 2012;158(1):46-61. doi:10.1111/j.1365-2141.2012.09128.x. **11** Wolff D, Schleuning M, von Harsdorf S, et al. Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. Biol Blood Marrow Transplant. 2011;17(1):1-17. doi:10.1016/j.bbmt.2010.05.011. **12** Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv30-iv40. doi:10.1093/annonc/mdy133. **13** Latzka J, Assaf C, Bagot M, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2023. Eur J Cancer. 2023;195:113343. doi:10.1016/j.ejca.2023.113343. **14** Gilson D, Whittaker SJ, Child FJ, et al. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Br J Dermatol. 2019;180(3):496-526. doi:10.1111/bjd.17240. **15** Connelly-Smith L. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue. Journal of clinical apheresis. 2023;38(2):77-278. doi:10.1002/jca.22043. **16** Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2023;42(5):e1-e141. doi:10.1016/j.healun.2022.10.015

Important Safety Information

IMPORTANT SAFETY INFORMATION FOR THE THERAKOS™ PHOTOPHERESIS PROCEDURE

Indications

The THERAKOS™ CELLEX™ Photopheresis System is indicated for patients older than 18 years of age for the administration of photopheresis in the following:

- Cutaneous T Cell Lymphoma (CTCL)
- Solid Organ Transplant Rejection (SOT) (heart, lung)

The THERAKOS™ CELLEX™ Photopheresis System is indicated in patients older than 3 years of age for the management of:

- Acute and Chronic Graft versus Host Disease (aGvHD, cGvHD)

Contraindications

THERAKOS™ Photopheresis is contraindicated in:

- Patients possessing a specific history of a light sensitive disease
- Patients who cannot tolerate extracorporeal volume loss or who have white blood cell counts greater than 25,000 / mm^3
- Patients who have coagulation disorders or who have previously had a splenectomy

Warnings and Precautions

THERAKOS™ Photopheresis treatments should always be performed in locations where standard medical emergency equipment is available. Volume replacement fluids and/or volume expanders should be readily available throughout the procedure.

- Do not expose the device to a magnetic resonance (MR) environment. The device may present a risk of projectile injury, and thermal injury and burns may occur. The device may generate artifacts in the MR image, or may not function properly.
- Thromboembolic events, including pulmonary embolism and deep vein thrombosis, have been reported in the treatment of Graft versus Host Disease (GvHD). Special attention to adequate anticoagulation is advised when treating patients with GvHD.
- When prescribing and administering THERAKOS™ Photopheresis for patients receiving concomitant therapy, exercise caution when changing treatment schedules to avoid increased disease activity that may be caused by abrupt withdrawal of previous therapy.

Adverse Events

- Hypotension may occur during any treatment involving extracorporeal circulation. Closely monitor the patient during the entire treatment for hypotension.
- Transient pyretic reactions, 37.7–38.9°C (100–102°F), have been observed in some patients within six to eight hours of reinfusion of the photoactivated leukocyte-enriched blood. A temporary increase in erythroderma may accompany the pyretic reaction.
- Treatment frequency exceeding labelling recommendations may result in anaemia.
- Venous access carries a small risk of infection and pain.

Please refer to the THERAKOS™ CELLEX™ Photopheresis System Operator's Manual for a complete list of warnings and precautions.

IMPORTANT SAFETY INFORMATION FOR METHOXSALEN USED IN CONJUNCTION WITH THERAKOS™ PHOTOPHERESIS

Consult the 8-methoxypsoralen (Methoxsalen (20 micrograms / mL)) professional leaflet or the oral 8-methoxypsoralen formulation package insert before prescribing or dispensing any medication.

Warnings and Precautions

- Patients exhibiting multiple basal cell carcinomas or having a history of basal cell carcinoma should be diligently observed and treated.
- Methoxsalen may cause fetal harm when given to a pregnant woman. Women undergoing photopheresis should be advised to avoid becoming pregnant.
- Special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitizing agents.
- Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic.
- Patients should be told emphatically to wear UVA absorbing, wrap-around sunglasses for twenty-four (24) hours after methoxsalen treatment. They should wear these glasses any time they are exposed to direct or indirect sunlight, whether they are outdoors or exposed through a window.

Refer to the package insert for methoxsalen sterile solution (20 micrograms / mL) or the oral 8-methoxypsoralen dosage formulation for a list of all warnings and precautions.

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For more information about THERAKOS ECP Immunomodulation™, please visit: www.therakos.eu

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